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Efficacy and harms of direct oral anticoagulants in the elderly for stroke prevention in atrial fibrillation and secondary prevention of venous thromboembolism: systematic review and meta-analysis

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Abstract

Background—Evidence regarding use of direct oral anticoagulants (DOACs) in the elderly, particularly bleeding risks, is unclear despite the presence of greater comorbidities, polypharmacy and altered pharmacokinetics in this age group.

Methods and Results—We performed a systematic review and meta-analysis of randomised trials of DOACs (dabigatran, apixaban, rivaroxaban, edoxaban) for efficacy and bleeding outcomes compared to VKA (vitamin k antagonists) in elderly participants (aged ≥75 years) treated for acute venous thromboembolism or stroke prevention in atrial fibrillation.

Nineteen studies were eligible for inclusion but only 11 reported data specifically for elderly participants. Efficacy in managing thrombotic risks for each DOAC was similar or superior to VKA in the elderly. A non-significantly, higher risk of major bleeding than VKA was observed with dabigatran 150mg (Odds Ratio 1.18, 95% confidence interval 0.97-1.44) but not with the 110mg dose. Significantly higher gastrointestinal bleeding risks with dabigatran 150mg (1.78, 1.35-2.35) and 110mg (1.40, 1.04-1.90) and lower intracranial bleeding risks than VKA for dabigatran 150mg (0.43, 0.26-0.72) and dabigatran 110mg (0.36, 0.22-0.61) were also observed. A significantly lower major bleeding risk compared to VKA was observed for apixaban (0.63,

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0.51-0.77), edoxaban 60mg (0.81, 0.67-0.98) and 30mg (0.46, 0.38-0.57) while rivaroxaban showed similar risk.

Conclusion—DOACs demonstrated at least equal efficacy to VKA in managing thrombotic risks in the elderly however bleeding patterns were distinct. In particular, dabigatran was associated with a higher risk of gastrointestinal bleeding than VKA. Insufficient published data for apixaban, edoxaban and rivaroxaban indicates further work is needed to clarify their bleeding risks in the elderly.

Keywords

elderly; anticoagulant; bleeding; atrial fibrillation; venous thromboembolism

Introduction

Advanced age is a significant risk factor for atrial fibrillation (AF) and venous thromboembolism (VTE).[1, 2] AF prevalence estimates are <0.1% in the population aged <55 years and rise to over 8% in those aged >80 years.[3] Patients with AF have a five-fold greater risk of stroke.[1, 4] The increased risk of VTE with age is also estimated to double with every decade after the age of 40.[5, 6] The major complication of VTE is recurrence.[7] Anticoagulant therapy is essential for managing these thrombotic risks, particularly in an ageing population who are at higher risk.

Vitamin K antagonists (VKA) have until recently been the only oral anticoagulant treatment option available for patients. However four direct oral anticoagulants (DOACs), dabigatran, rivaroxaban, apixaban and edoxaban have now undergone trials to investigate their harm for use and efficacy in the management of thromboembolic risk in AF and acute VTE. They have been adopted into clinical practice as they confer certain practical advantages over VKA.[8] They are reported to have less drug-drug and drug-food interactions and have been licensed for use without the need for routine monitoring of anticoagulation effect. This is due to their predictable pharmacokinetic profiles.[9] However, as for VKA, they pose a significant risk of bleeding which is complicated further by the lack of a reversal agent.[10]

Though several reviews have evaluated the efficacy and harms of DOACs in the general population,[11, 12] the specific evidence base for their use in the elderly aged ≥75 years remains unclear. The risk of harm with DOACs compared to VKA, in particular bleeding risks, warrants clarity given the presence of greater comorbidities, polypharmacy and altered pharmacokinetics in the elderly.[13]

We undertook a systematic review and meta-analysis of randomised controlled trials for use of the DOACs in the management of AF and acute VTE, where VKA were used as a comparator. No randomised controlled trial for DOACs has been conducted thus far that involves only elderly participants. Hence, our approach was to evaluate the DOACs for efficacy and harms compared to VKA in the elderly participants aged ≥75 years from each trial. These results were then put in context by presenting the results from the total trial populations (all ages), based on which marketing authorisations for DOACs have been granted.

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Methods

Eligibility Criteria

We identified all phase II and III randomised controlled trials of the DOACs (dabigatran 150mg and 110mg, apixaban, rivaroxaban and edoxaban 60mg and 30mg) in patients being treated for acute VTE (deep vein-thrombosis and/or pulmonary embolism) and for stroke prevention in AF. We required that studies have a minimum of 3 months patient follow-up and used VKA as a comparator. For phase II studies, we extracted data for doses that were used for subsequent phase III clinical trials only. We excluded studies if they were extensions of previously completed trials for additional follow-up.

Search Strategy

Medline, Embase and CENTRAL (Cochrane central register of controlled trials) were searched for articles in English from 22nd November 1993 to 22nd November 2013. The search was subsequently updated to June 1st 2014. Search strategies for each database are presented in the Supplementary Material. Clinical trial registries were also searched and conference proceedings were identified using web of science, scopus and international pharmacy abstracts. Additional studies, including unpublished and grey literature were identified by screening reference lists of retrieved studies and review articles. In instances where subgroup data for elderly patients aged ≥75 years was unpublished, drug manufacturers, authors and relevant regulatory bodies e.g. US FDA (United States Food and Drug safety Administration) and EMA (European Medicines Agency) were contacted to request the data. The search strategy was checked for appropriateness by a second investigator.

Study Selection

One reviewer (MS) performed the full search strategy, removed duplicates and selected the articles. One of three other independent reviewers (VC, JP, JGD) analysed these selections for eligibility of inclusion. Studies were screened based on title and abstract initially, following which full texts were obtained and assessed for inclusion.

Data Extraction

All data was extracted by two reviewers (MS with VC, JP or JGD) independently into standardised forms and entered into Microsoft Excel®. Data extracted included study details, participant details, intervention details (drug name, dose, frequency) and comparator details (time in therapeutic range). Data was collected for the subgroup of elderly patients aged ≥75 years and the total trial population (all ages) for each study. The intention to treat populations were used where possible. Primary efficacy outcomes were stroke or systemic embolism for AF trials, and recurrent venous thromboembolism for VTE studies. The primary safety outcome was pooled major bleeding from both AF and VTE studies. Secondary outcomes were gastrointestinal bleeding, intracranial bleeding, clinically relevant bleeding and fatal bleeding. Studies were also assessed for potential bias (low, unclear, high) using the Cochrane Collaboration's risk of bias assessment.[14] All disagreements between reviewers were resolved by consensus or discussion with a third reviewer.

Statistical Analyses

The treatment effect for DOAC compared to VKA was estimated by meta-analyses for each drug separately (dabigatran 150mg and 110mg, apixaban, rivaroxaban and edoxaban 60mg and 30mg). This was undertaken for elderly participants aged ≥75 years for each outcome of interest. It was then repeated for the total trial participants to allow comparison. Data synthesis was invariably undertaken using a Peto Odds ratio fixed effect model.[15] However, when there was high heterogeneity with greater than 4 studies contributing to the estimate; a random effects model (DerSimonian and Laird) was used. [16] Use of a random effects model to determine estimates is highlighted in the results through use of the annotation "Random Effects" in brackets alongside the odds ratio estimate. Study heterogeneity was analysed using the I-squared statistic. Sensitivity analysis was undertaken by indication, mean duration of patient follow up (<6months vs ≥6months) and where high heterogeneity (>75%) was evident. A funnel plot was used to assess publication bias. The manuscript was prepared in accordance with the preferred reporting items for systematic reviews and meta-analysis (PRISMA).[17] All analyses were performed using Review Manager® software (Rev Man 5.2®). Where only confidence intervals were available for outcomes, event rates were calculated using the method detailed by Tierney and colleagues.[18]

Results

Our search identified 19 multi-centred, randomised controlled trials eligible for inclusion with 11 reporting data on elderly patients as shown in Supplemental Figure 1. Detailed rationale behind exclusion of studies is presented in Supplemental Table S1. Additional unpublished data was requested for all 19 studies from manufacturers, authors and regulatory authorities but only data for 4/19 (21.0%) studies was obtained.[19-22] Additional data from documentation published by regulatory authorities and conference proceedings for 6/19 (31.6%) studies was also retrieved.[19, 20, 23-26]

Study Characteristics

Eleven phase III and 8 phase II studies consisting of 5 dabigatran trials,[24, 27-30] 4 apixaban trials,[26, 31-33] 5 rivaroxaban trials,[19-23] and 5 edoxaban trials.[25, 34-37] All studies used warfarin as comparator with 4 studies also allowing use of other VKAs.[19, 20, 23, 33] Follow-up periods were longest for the phase III AF studies as shown in Table 1. Included studies mostly used definitions for major bleeding as per International Society of Thrombosis and Haemostasis,[38] while two phase II studies used a slight variation of this definition.[25, 36] Definitions used to classify clinically relevant bleeding showed minimal variation and essentially consisted of a major bleed or any overt bleeding event that did not meet the criteria for major bleeding but led to either hospital admission for bleeding, physician-guided treatment or an alteration in therapy. Intracranial and fatal bleeding were both included as part of the major bleeding events. Gastrointestinal bleeding was recorded also as either a major or clinically relevant bleed based on independent adjudication in each study.

Patient Characteristics

Data was reported for 31,418 elderly participants aged ≥75 years out of a total of 102,479 participants aged ≥18 years. Mean age ranged from 64.5 to 71.7 years in AF studies and

54.4 to 59.0 years in VTE studies (Table 2). Mean $CHADS_2$ for AF studies ranged from 1.8 to 3.5 where reported while percentage of patients recruited with a history of a previous VTE ranged from 15.8% to 29.0% in the VTE studies. The Rocket-AF study recruited patients with the highest $CHADS_2$ scores of 3.5 in each arm.[22] The dabigatran study, Recover I, was the phase III study that recruited the highest percentage of patients with previous VTE for DOAC (25.7%) and VKA (25.4%) therapy respectively.[28] All studies permitted usage of aspirin if necessary with DOAC, however the percentage of patients on aspirin in individual studies was inadequately reported as shown in Supplemental Table S2.

Risk of Bias Assessment

Results of the risk of bias assessment for all 19 studies are presented in Figure 1. Eleven studies were open-label and at high risk of bias from lack of blinding of patients and personnel to the intervention.[19, 20, 23-25, 27, 30, 32, 33, 36, 37] However, all studies where reported were assessed by blinded adjudicators for the outcomes. Two studies were deemed to be at high risk of bias from incomplete outcome data due to unclear attrition.[22, 23] In both Rocket-AF and Einstein-DVT dose,[22, 23] 93 patients were omitted from analysis due to protocol violations. Bibr 1048 was judged to be at risk of other bias because a full publication for the trial was not available.[24] The funnel plots as shown in Figure 2 for the total population indicate we obtained a reasonable expected balance of positive and negative results from the included studies. Only 11 studies reported data on the elderly population hence assessment of publication bias was challenging. Data was requested from the pharmaceutical companies and regulatory bodies where elderly subgroup data had not been reported. However, only limited data was made available.

Outcomes

Primary Efficacy Outcomes—Each DOAC was shown to be at least as effective as VKA in the elderly. This was both in reducing risk of stroke or systemic embolism in AF, and risk of recurrent venous thromboembolism in VTE. Efficacy observed was also similar to that seen in the total population (all ages).

In AF studies, a significant reduction in risk of stroke or systemic embolism compared to VKA was observed for dabigatran 150mg (Odds Ratio 0.66, 95% confidence interval 0.49-0.90; p=0.009) and apixaban (OR 0.70, 95% CI 0.52-0.93; p=0.01). This significant risk reduction was also maintained in the total populations for both DOACs (Figure 3).

Results in the elderly for all four DOACs in reducing risk of recurrent VTE are shown in Figure 4. These estimates were limited by low event rates but did not indicate inferiority compared to VKA. Results from the total population also supported non-inferiority to VKA.

Primary Safety Outcome

Major bleeding: In the elderly, a significant reduction in risk of major bleeding compared to VKA was observed for for apixaban (OR 0.63, 95% CI 0.51-0.77; p<0.0001), edoxaban 60mg (OR 0.81, 95% CI 0.67-0.98; p=0.03) and 30mg (OR 0.46, 95% CI 0.38-0.57; p<0.0001). The superiority to VKA for these DOACs was also observed in the total population (Figure 5).

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Dabigatran 150mg showed a non-significant, higher risk of major bleeding compared to VKA in the elderly (OR 1.18, 95% CI 0.97-1.44; p=0.10); though risk was similar to VKA with the 110mg dose. In contrast in the total population, a non-significant lower risk than VKA was observed with the 150mg dose; while a significantly lower risk was observed with the 110mg dose.

Secondary Outcomes

Gastrointestinal bleeding: In the elderly, gastrointestinal bleeding was significantly increased compared to VKA with dabigatran 150mg (OR 1.78, 95% CI 1.35-2.35; p<0.0001) and 110mg (OR 1.40, 95% CI 1.04-1.90; p=0.03) (Figure 6). Data regarding risk of gastrointestinal bleeding in the elderly for the other DOACs was not published or made available.

For the total population: the significantly increased risk of gastrointestinal bleeding compared to VKA was sustained with dabigatran 150mg, but not with the 110mg dose. In the total population, rivaroxaban and edoxaban 60mg also showed a significantly higher risk of gastrointestinal bleeding than VKA.

Intracranial bleeding: In the elderly, a significant reduction in risk of intracranial bleeding compared to VKA was observed for dabigatran 150mg (OR 0.43, 95% CI 0.26-0.72; p=0.001) dabigatran 110mg (OR 0.36, 95% CI 0.22-0.61; P=0.0001) and apixaban (OR 0.38, 95% CI 0.24-0.59; p<0.0001). A non-significant reduction was also observed for rivaroxaban while data was not available for edoxaban in the elderly.

In the total population all DOACS showed a significantly lower risk of intracranial bleeding compared to VKA as shown in Figure 6.

Clinically Relevant Bleeding: In the elderly, the risk of clinically relevant bleeding where reported was not significantly different for DOACs compared to VKA; except for apixaban, which demonstrated superiority to VKA; (OR 0.64, 95% CI 0.54-0.76; p<0.0001; Random Effects).

In the total population, apixaban, dabigatran 150mg and edoxaban 60mg and 30mg demonstrated superiority to VKA in reducing this risk (Figure 6).

Fatal Bleeding: In the elderly, the risk of fatal bleeding where reported was not significantly different for DOACs to VKA; except for rivaroxaban which showed superiority (OR 0.53, 95% CI 0.30-0.93; p=0.03). Data for this outcome was limited by the low number of fatal bleeding events in the studies. No data was available for edoxaban.

In the total population, a significantly reduced risk of fatal bleeding compared to VKA was observed for dabigatran 110mg, rivaroxaban, edoxaban 60mg, and edoxaban 30mg (Figure 6).

Heterogeneity Assessment and Sensitivity Analysis

Significant heterogeneity (I^2>75%) was found when all four DOACs were pooled together and compared to VKA for major bleeding, gastrointestinal bleeding and fatal bleeding. Moderate heterogeneity (I^2=50-75%) was found for risk of stroke or systemic embolism and intracranial bleeding. Sensitivity analysis undertaken by removing the only direct thrombin inhibitor, dabigatran, and leaving in the three factor Xa inhibitors showed similar high heterogeneity across outcomes. Investigation indicated that this high heterogeneity may be due to either differing baseline bleeding risks in the studies or true differences between each DOAC which, when pooled, were masked. This is why results for all four DOACs pooled together compared to VKA are not presented.

There was evidence of statistical heterogeneity in the estimate for risk of major bleeding compared to VKA for rivaroxaban in the elderly (I^2=82%). This was largely attributable to the unusually high number of bleeding events in the VKA arm in Einstein PE compared to the other three rivaroxaban AF and VTE studies. Heterogeneity was also present for the estimate for risk of clinically relevant bleeding for apixaban in the total population (I^2=81%). Sensitivity analysis did not yield a satisfactory source for this heterogeneity. Hence, a random effects model was applied.[16] No other outcome estimate produced significant heterogeneity.

Additional sensitivity analysis by indication and mean duration of patient follow up did not significantly alter interpretation of findings in the elderly except in the case of rivaroxaban for major bleeding. For rivaroxaban, in AF the major bleeding risk was (OR 1.17, 95%CI 0.95-1.43) and in VTE it was (OR 0.30, 95%CI 0.15-0.58).

Discussion

This systematic review and meta-analysis investigating use of DOACs in AF and VTE has shown that they are at least as effective as VKA in the elderly aged ≥75 years. Similar efficacy was also seen in the elderly and total trial populations (all ages). The meta-analysis of bleeding risks with DOACs has shown them to be distinct to VKA. For the direct thrombin inhibitor, dabigatran, risks also appeared to differ for bleeding between elderly and total trial populations. Dabigatran 150mg showed a non-significantly higher risk of major bleeding than VKA in the elderly. However, in the total population a reduction in major bleeding was observed with dabigatran compared to VKA which was significant for the 110mg dose. Two of the direct factor Xa inhibitors (apixaban and edoxaban) showed a lower major bleeding risk to VKA in both the elderly and total population; while rivaroxaban showed a similar risk.

Elderly patients taking either dose of dabigatran were at higher risk of gastrointestinal bleeding than those on VKA; this risk was also present in the total populations but with the 150mg dose only. Use of DOACs provided a protective effect compared to VKA against intracranial bleeding in the elderly that was consistent with the total population. Results where available for clinically relevant bleeding, or fatal bleeding for DOACs did not suggest different risks to VKA in the elderly. However, interpretation of these secondary bleeding outcomes in the elderly was limited by the low numbers of elderly patients with bleeding

events in the studies. This was compounded by the fact that all data requested from pharmaceutical manufacturers and regulatory authorities we approached was not made available.

The intention from our protocol was to provide pooled outcome data for all four DOACs together versus VKA as well. However, we found significant heterogeneity when the drugs were combined for several outcomes. This appeared to be due to either differing baseline bleeding risks in the studies or true differences between each drug. Hence, this result was not deemed appropriate to present.

Our choice of the total trial population as our reference group for contextualising the results in the elderly was based on guidance in the Cochrane handbook on conducting subgroup meta-analysis in trials.[14] Comparing two subgroup meta-analyses, ages ≥75 to <75 for example, based purely on statistical significance of subgroup results would have been misleading as both analyses are likely to have different abilities to detect effects. Hence, we did not choose the <75 population as our main reference though we have included the meta-analysis for the <75 population in the supplementary appendix online.

The sub-group analysis of the dabigatran Phase III, Re-ly trial suggested that major bleeding risk may increase with age for dabigatran.[39] Our study has suggested, however that this risk increase is not significantly greater than VKA. Dabigatran relies more on renal excretion for elimination than the other three DOACs. Given that renal function declines with age, this may be a factor for greater bleeding risk.[40] However, renal function alone cannot fully explain this variation in bleeding risk which is likely to be influenced by other unverified age-related factors as well.

The increased risk of gastrointestinal bleeding and associated mortality with age has been well established.[41] Use of anticoagulant medication is known to increase this risk further.[42] Gastrointestinal bleeding was found to significantly increase with rivaroxaban, edoxaban 60mg and dabigatran 150mg compared to VKA in the total population. This risk increased further for dabigatran in the elderly. Gastrointestinal bleeding risks with other DOACs in the elderly could not be examined due to the lack of availability of data. This was a serious concern given that gastrointestinal bleeding has been shown both in this study and previous work to be a significant risk with usage of DOACs.

Use of VKA and advanced age are both strong predictive factors for intracranial bleeding.[43] The protective benefit against intracranial bleeding that the DOACs confer over VKA in the general population did not appear to be lost in the elderly. Given that intracranial bleeding is one of the major factors responsible for mortality resulting from complications of VKA usage, this finding was significant.[43]

It is worth noting that the pooled bleeding results in this study are heavily weighted towards the large pivotal phase III AF study for each of the four DOACs.[22, 26, 27, 35] As a result, the respective trial populations in these studies should be considered. Notably, the population in the edoxaban (Engage-AF-Timi48),[35] and rivaroxaban study (Rocket-AF),[22] both had higher mean $CHADS_2$ risk scores of 2.8 and 3.5 respectively compared to 2.1 in both the dabigatran (Re-ly)[27] and apixaban (Aristotle)[26] studies. The $CHADS_2$ risk assessment tool

can help predict risk of stroke in patients with AF,[44] and indicated inclusion of a lower risk population in Re-ly and Aristotle. Mean time in therapeutic range (TTR) on VKA did vary across the four studies (55.0%-64.9%); and Rocket-AF was lowest with 55%. Such deviations in TTR are, however also common in clinical practice.[45] These differences in the trial populations mean comparisons between DOACs can be misleading and were not undertaken here. Until head to head clinical trials comparing the DOACs against one another are conducted, it will not be possible to know which DOAC has the best efficacy and harm profile in the elderly or total populations.

Research in Context

This is the first study that has attained and assessed all available evidence for dabigatran, apixaban, rivaroxaban and edoxaban in AF and VTE treatment in the elderly from literature, regulatory bodies and drug manufacturers. The DOACs have been tested for other indications such as thromboprophylaxis following hip and knee replacements. However, these studies used different doses and comparators and hence were not eligible for inclusion.[46]

"Real world" data is gradually emerging for the DOACs though such observational data can be subject to confounding. [47-49] Studies investigating the risks of dabigatran thus far have produced conflicting results.[48, 49] A Danish cohort study for example, found significantly worse bleeding patterns with dabigatran 110mg in the total population than seen in this analysis.[49] Two small studies also highlighted how bleeding risks in particular in the elderly remain a significant concern with dabigatran.[50, 51] As further information emerges from larger studies such as the prospective DOAC register in Dresden, harms and benefits for DOACs in the elderly will become clearer.[52]

Limitations of this study

Interpretation of subgroup data from clinical trials for elderly patients aged ≥75 years requires caution as trials were not initially powered to detect these differences. Randomisation in studies was not stratified by age; hence it was not possible to ensure all confounders such as concomitant aspirin usage or impaired renal function were balanced across arms. Population sizes for primary outcomes, however were reasonably large. Our data was also limited by lack of published results in the public domain or available from regulatory authorities and manufacturers. This meant that several summary estimates in the elderly were based on only one or two studies. Due to the lack of patient level data, we were unable to ascertain the age distribution of our elderly participants and number of 'frail' elderly patients aged above 80 and 85 years that had actually been included.

Outcome data on cardiovascular events was not reported. A signal for increased risk of myocardial infarction with dabigatran compared to VKA has been previously raised.[53] However, a large post-marketing surveillance study completed by the FDA has not found this risk to be significant.[54]

In the VTE studies, it was common for patients to receive several days (median 2-9 days) of a heparin before beginning treatment with either a DOAC or VKA.[28, 29, 34] In Amplify, Einstein- DVT and Einstein-PE they received a higher dose of oral anticoagulant for a short

period prior to initiation of standard DOAC dose.[19, 20, 31] Also, as bleeding definitions were not mutually exclusive within trials; some estimates of risk by bleeding classification were difficult to interpret. These factors could ultimately affect the precision of bleeding estimates. Follow-up did vary between studies, however all had at least 3 months and covered the initial period during which harm has been found to be highest with usage of anticoagulants.[55]

Conclusion

DOACs showed at least equal efficacy to VKA in the elderly for acute VTE and AF. However, bleeding patterns seen with DOACs were different. Dabigatran, in particular, showed a significantly higher risk of gastrointestinal bleeding and a non-significantly higher major bleeding risk than VKA. This suggests that caution is required in prescribing where there may be concomitant risk factors for gastrointestinal bleeding in the elderly. A benefit of reduced intracranial bleeding was seen with dabigatran, apixaban and rivaroxaban.

Insufficient published data for apixaban, edoxaban and rivaroxaban meant all bleeding risks, particularly gastrointestinal risks, could not be fully explored in the elderly. Better availability of unpublished trial data and more research is needed to elucidate risks further.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, D'Agostino RB, Massaro JM, Beiser A, Wolf PA, Benjamin EJ. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. Circulation. 2004; 110:1042–6. [PubMed: 15313941]
2. Kyrle PA, Eichinger S. Clinical scores to predict recurrence risk of venous thromboembolism. Thromb Haemost. 2012; 108:1061–4. [PubMed: 22872143]
3. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA. 2001; 285:2370–5. [PubMed: 11343485]
4. Vidaillet H, Granada JF, Chyou Po-H, Maassen K, Ortiz M, Pulido JN, Sharma P, Smith PN, Hayes J. A population-based study of mortality among patients with atrial fibrillation or flutter. The American Journal of Medicine. 2002; 113:365–70. [PubMed: 12401530]
5. Anderson FA Jr. Spencer FA. Risk factors for venous thromboembolism. Circulation. 2003; 107:I9–16. [PubMed: 12814980]
6. Goldhaber SZ. Risk factors for venous thromboembolism. J Am Coll Cardiol. 2010; 56:1–7. [PubMed: 20620709]

7. Kearon C. Natural history of venous thromboembolism. Semin Vasc Med. 2001; 1:27–37. [PubMed: 15199511]
8. Wise J. NICE backs new oral anticoagulant for stroke prevention. BMJ. 2012; 344
9. Heidbuchel H, Verhamme P, Alings M, Antz M, Hacke W, Oldgren J, Sinnaeve P, Camm AJ, Kirchhof P. EHRA practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary. Eur Heart J. 2013; 34:2094–106. [PubMed: 23625209]
10. Wallace H, Davies MW. The lack of antidotes for new oral anticoagulants. BMJ. 2014; 348
11. Castellucci LA, Cameron C, Gal GL, Rodger MA, Coyle D, Wells PS, Clifford T, Gandara E, Wells G, Carrier M. Efficacy and safety outcomes of oral anticoagulants and antiplatelet drugs in the secondary prevention of venous thromboembolism: systematic review and network meta-analysis. BMJ. 2013; 347
12. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T, Antman EM. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014; 383:955–62. [PubMed: 24315724]
13. McLean AJ, Le Couteur DG. Aging Biology and Geriatric Clinical Pharmacology. Pharmacol Rev. 2004; 56:163–84. [PubMed: 15169926]
14. Higgins, J.; Green, S., editors. [Accessed July 4, 2014] Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration 2011. http://www.cochrane-handbook.org/
15. Bradburn MJ, Deeks JJ, Berlin JA, Russell Localio A. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. Stat Med. 2007; 26:53–77. [PubMed: 16596572]
16. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986; 7:177–88. [PubMed: 3802833]
17. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009; 339
18. Tierney J, Stewart L, Ghersi D, Burdett S, Sydes M. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007; 8:16. [PubMed: 17555582]
19. Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS, Lensing AW, Misselwitz F, Prins MH, Raskob GE, Segers A, Verhamme P, Wells P, Agnelli G, Bounameaux H, Cohen A, Davidson BL, Piovella F, Schellong S. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010; 363:2499–510. [PubMed: 21128814]
20. Buller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, Minar E, Chlumsky J, Verhamme P, Wells P, Agnelli G, Cohen A, Berkowitz SD, Bounameaux H, Davidson BL, Misselwitz F, Gallus AS, Raskob GE, Schellong S, Segers A. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med. 2012; 366:1287–97. [PubMed: 22449293]
21. Hori M, Matsumoto M, Tanahashi N, Momomura S, Uchiyama S, Goto S, Izumi T, Koretsune Y, Kajikawa M, Kato M, Ueda H, Iwamoto K, Tajiri M. Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation - the J-ROCKET AF study. Circ J. 2012; 76:2104–11. [PubMed: 22664783]
22. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KAA, Califf RM. Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. N Engl J Med. 2011; 365:883–91. [PubMed: 21830957]
23. Buller HR, Lensing AW, Prins MH, Agnelli G, Cohen A, Gallus AS, Misselwitz F, Raskob G, Schellong S, Segers A. A dose-ranging study evaluating once-daily oral administration of the factor Xa inhibitor rivaroxaban in the treatment of patients with acute symptomatic deep vein thrombosis: the Einstein-DVT Dose-Ranging Study. Blood. 2008; 112:2242–7. [PubMed: 18621928]

24. Boehringer Ingelheim. [Accessed June 4, 2014] A Dose Response Study of Dabigatran Etexilate(BIBR 1048) in Pharmacodynamics and Safety in Patients with Non-valvular Atrial Fibrillation in Comparison to Warfarin NCT01136408. http://www.clinicaltrials.gov/ct2/show/NCT01136408
25. Chung N, Jeon HK, Lien LM, Lai WT, Tse HF, Chung WS, Lee TH, Chen SA. Safety of edoxaban, an oral factor Xa inhibitor, in Asian patients with non-valvular atrial fibrillation. Thromb Haemost. 2011; 105:535–44. [PubMed: 21136011]
26. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FWA, Zhu J, Wallentin L. Apixaban versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med. 2011; 365:981–92. [PubMed: 21870978]
27. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener H-C, Joyner CD, Wallentin L. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med. 2009; 361:1139–51. [PubMed: 19717844]
28. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, Baanstra D, Schnee J, Goldhaber SZ. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med. 2009; 361:2342–52. [PubMed: 19966341]
29. Schulman S, Kakkar AK, Goldhaber SZ, Schellong S, Eriksson H, Mismetti P, Christiansen AV, Friedman J, Le Maulf F, Peter N, Kearon C. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. Circulation. 2014; 129:764–72. [PubMed: 24344086]
30. Ezekowitz MD, Reilly PA, Nehmiz G, Simmers TA, Nagarakanti R, Parcham-Azad K, Pedersen KE, Lionetti DA, Stangier J, Wallentin L. Dabigatran with or without concomitant aspirin compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO Study). Am J Cardiol. 2007; 100:1419–26. [PubMed: 17950801]
31. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Masiukiewicz U, Pak R, Thompson J, Raskob GE, Weitz JI. Oral Apixaban for the Treatment of Acute Venous Thromboembolism. N Engl J Med. 2013; 369:799–808. [PubMed: 23808982]
32. Ogawa S, Shinohara Y, Kanmuri K. Safety and efficacy of the oral direct factor xa inhibitor apixaban in Japanese patients with non-valvular atrial fibrillation. -The ARISTOTLE-J study. Circ J. 2011; 75:1852–9. [PubMed: 21670542]
33. Buller H, Deitchman D, Prins M, Segers A. Efficacy and safety of the oral direct factor Xa inhibitor apixaban for symptomatic deep vein thrombosis. The Botticelli DVT dose-ranging study. J Thromb Haemost. 2008; 6:1313–8. [PubMed: 18541000]
34. Buller HR, Decousus H, Grosso MA, Mercuri M, Middeldorp S, Prins MH, Raskob GE, Schellong SM, Schwocho L, Segers A, Shi M, Verhamme P, Wells P. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med. 2013; 369:1406–15. [PubMed: 23991658]
35. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Špinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM. Edoxaban versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med. 2013; 369:2093–104. [PubMed: 24251359]
36. Weitz JI, Connolly SJ, Patel I, Salazar D, Rohatagi S, Mendell J, Kastrissios H, Jin J, Kunitada S. Randomised, parallel-group, multicentre, multinational phase 2 study comparing edoxaban, an oral factor Xa inhibitor, with warfarin for stroke prevention in patients with atrial fibrillation. Thromb Haemost. 2010; 104:633–41. [PubMed: 20694273]
37. Yamashita T, Koretsune Y, Yasaka M, Inoue H, Kawai Y, Yamaguchi T, Uchiyama S, Matsumoto M, Ogawa S. Randomized, multicenter, warfarin-controlled phase II study of edoxaban in Japanese patients with non-valvular atrial fibrillation. Circ J. 2012; 76:1840–7. [PubMed: 22664798]
38. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost. 2005; 3:692–4. [PubMed: 15842354]

39. Eikelboom JW, Wallentin L, Connolly SJ, Ezekowitz M, Healey JS, Oldgren J, Yang S, Alings M, Kaatz S, Hohnloser SH, Diener H-C, Franzosi MG, Huber K, Reilly P, Varrone J, Yusuf S. Risk of Bleeding With 2 Doses of Dabigatran Compared With Warfarin in Older and Younger Patients With Atrial Fibrillation: An Analysis of the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) Trial. Circulation. 2011; 123:2363–72. [PubMed: 21576658]
40. Stangier J. Clinical pharmacokinetics and pharmacodynamics of the oral direct thrombin inhibitor dabigatran etexilate. Clin Pharmacokinet. 2008; 47:285–95. [PubMed: 18399711]
41. Rockall TA, Logan RFA, Devlin HB, Northfield TC. Incidence of and mortality from acute upper gastrointestinal haemorrhage in the United Kingdom. BMJ. 1995; 311:222–6. [PubMed: 7627034]
42. Yachimski PS, Friedman LS. Gastrointestinal bleeding in the elderly. Nature Clinical Practice *Gastroenterology and Hepatology*. 2008; 5:80–93.
43. Rosand J, Eckman MH, Knudsen KA, Singer DE, Greenberg SM. The effect of warfarin and intensity of anticoagulation on outcome of intracerebral hemorrhage. Arch Intern Med. 2004; 164:880–4. [PubMed: 15111374]
44. Olesen JB, Lip GYH, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, Selmer C, Ahlehoff O, Olsen A-MS, Gislason GH, Torp-Pedersen C. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ. 2011; 342
45. Rose AJ, Hylek EM, Ozonoff A, Ash AS, Reisman JI, Berlowitz DR. Risk-adjusted percent time in therapeutic range as a quality indicator for outpatient oral anticoagulation: results of the Veterans Affairs Study to Improve Anticoagulation (VARIA). Circ Cardiovasc Qual Outcomes. 2011; 4:22–9. [PubMed: 21098779]
46. Gomez-Outes A, Terleira-Fernandez AI, Suarez-Gea ML, Vargas-Castrillon E. Dabigatran, rivaroxaban, or apixaban versus enoxaparin for thromboprophylaxis after total hip or knee replacement: systematic review, meta-analysis, and indirect treatment comparisons. BMJ. 2012; 344:e3675. [PubMed: 22700784]
47. Laliberte F, Cloutier M, Nelson WW, Coleman CI, Pilon D, Olson WH, Damaraju CV, Schein JR, Lefebvre P. Real-world comparative effectiveness and safety of rivaroxaban and warfarin in nonvalvular atrial fibrillation patients. Curr Med Res Opin. 2014; 30:1317–25. [PubMed: 24650301]
48. Larsen TB, Rasmussen LH, Skjøth F, Due KM, Callréus T, Rosenzweig M, Lip GYH. Efficacy and Safety of Dabigatran Etexilate and Warfarin in “Real-World” Patients With Atrial FibrillationA Prospective Nationwide Cohort Study. J Am Coll Cardiol. 2013; 61:2264–73. [PubMed: 23562920]
49. Sørensen R, Gislason G, Torp-Pedersen C, Olesen JB, Fosbøl EL, Hvidtfeldt MW, Karasoy D, Lamberts M, Charlot M, Køber L, Weeke P, Lip GYH, Hansen ML. Dabigatran use in Danish atrial fibrillation patients in 2011: a nationwide study. BMJ Open. 2013; 3
50. Yates SW. Novel oral anticoagulants for stroke prevention in atrial fibrillation: a focus on the older patient. Int J Gen Med. 2013; 6:167–80. [PubMed: 23687449]
51. Rajdev A, Bradley J, Petrini J, Alexander J. A Community experience of the novel anticoagulant Pradaxa. J Am Coll Cardiol. 2012; 59:E601–E.
52. Beyer-Westendorf J, Gelbricht V, Forster K, Ebertz F, Kohler C, Werth S, Kuhlisch E, Stange T, Thieme C, Daschkow K, Weiss N. Peri-interventional management of novel oral anticoagulants in daily care: results from the prospective Dresden NOAC registry. Eur Heart J. 2014; 35:1888–96. [PubMed: 24394381]
53. Artang R, Rome E, Nielsen JD, Vidaillet HJ. Meta-analysis of randomized controlled trials on risk of myocardial infarction from the use of oral direct thrombin inhibitors. Am J Cardiol. 2013; 112:1973–9. [PubMed: 24075284]
54. US Food and Drug Administration (FDA). [Accessed June 4, 2014] FDA Drug Safety Communication: FDA study of Medicare patients finds risks lower for stroke and death but higher for gastrointestinal bleeding with Pradaxa (dabigatran) compared to warfarin – 13 May 2014. http://www.fda.gov/Drugs/DrugSafety/ucm396470.htm

55. Hylek EM, Evans-Molina C, Shea C, Henault LE, Regan S. Major Hemorrhage and Tolerability of Warfarin in the First Year of Therapy Among Elderly Patients With Atrial Fibrillation. Circulation. 2007; 115:2689–96. [PubMed: 17515465]

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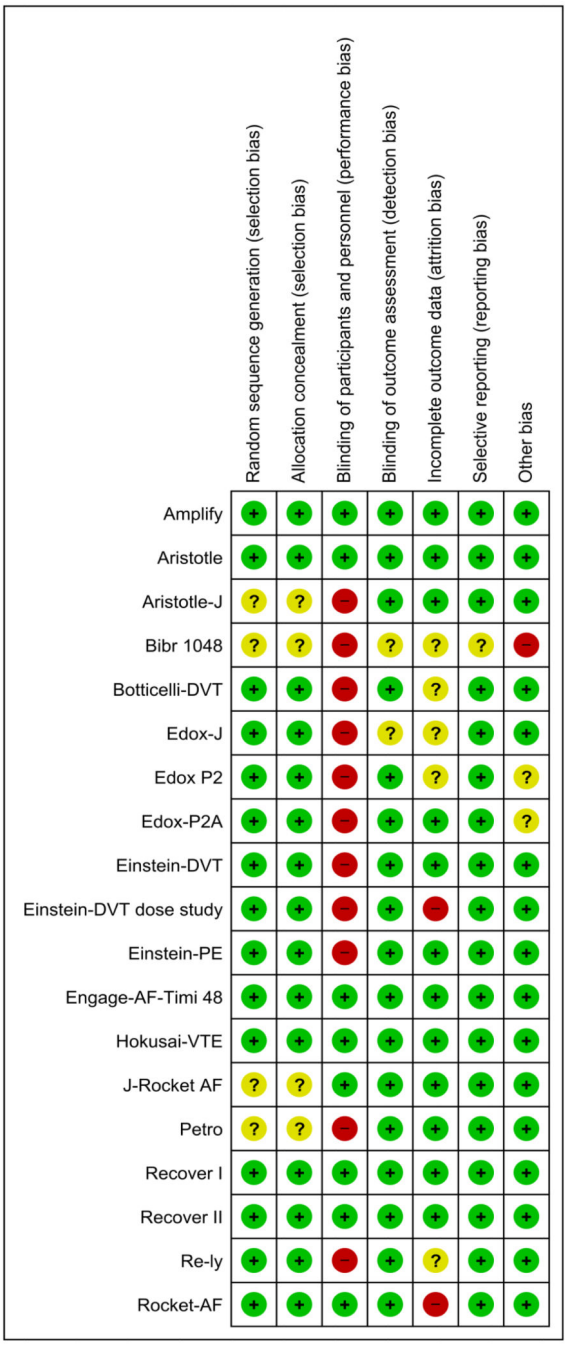

Figure 1. Summary of risk of bias assessment

Green(+) =Low bias risk; Red (−)=High bias risk; Yellow(?)=Unclear bias risk

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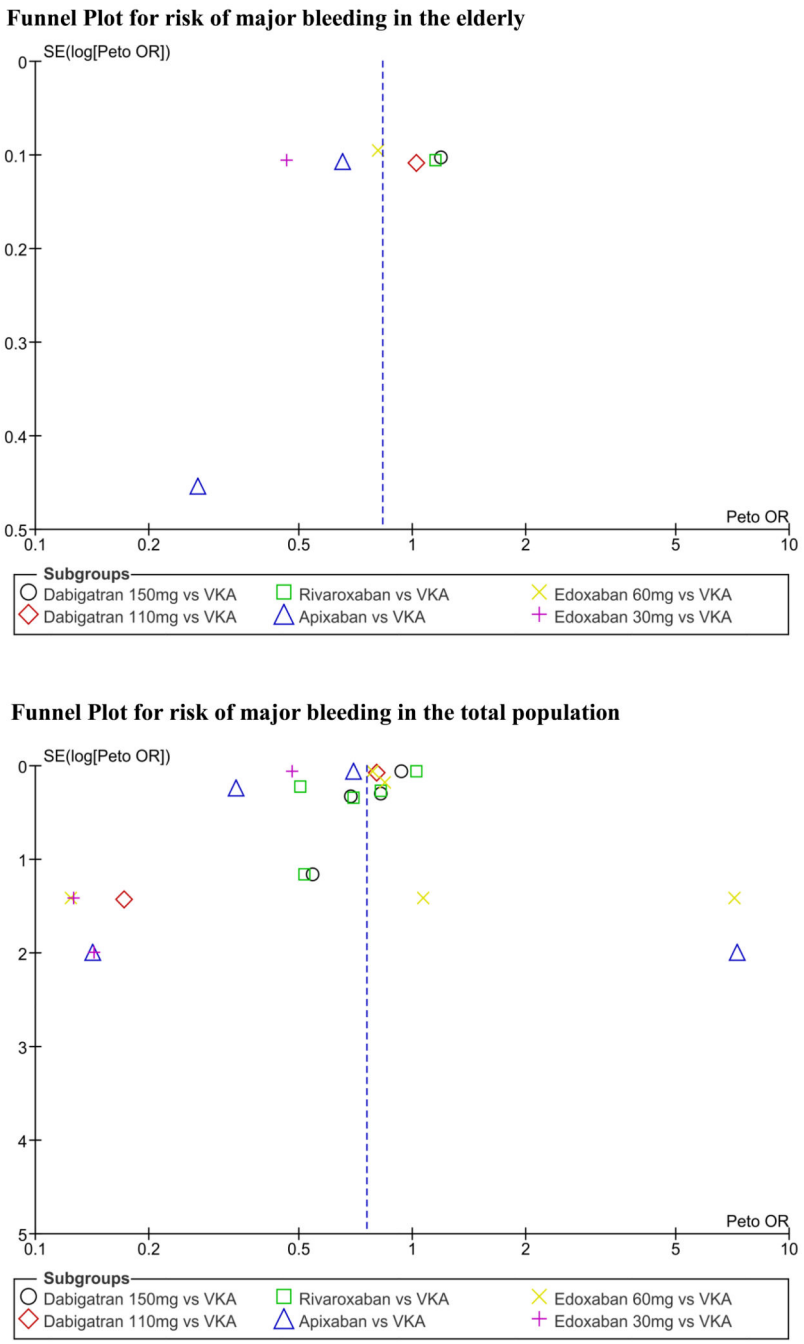

Figure 2. Funnel Plot Comparison for risk of major bleeding in the elderly (top) and total population (below)

*Note: Y axis scales differ between plots above.

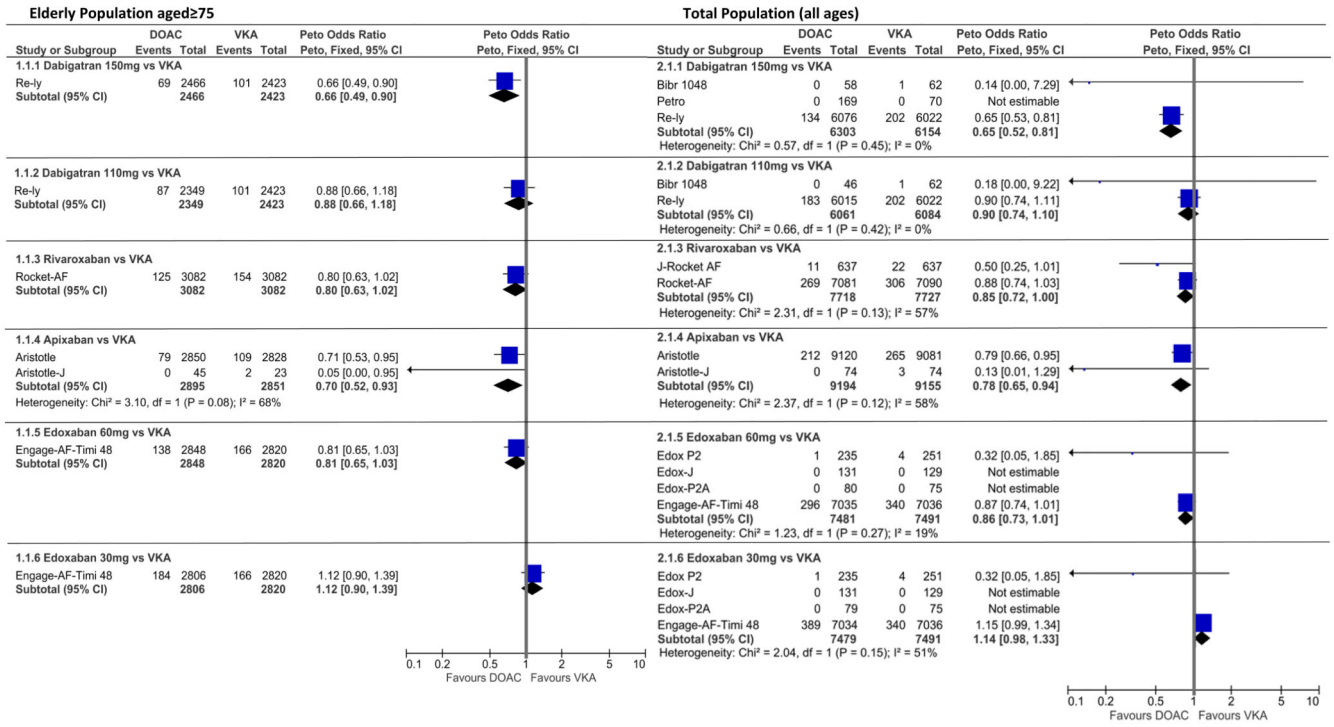

Figure 3. Risk of stroke or systemic embolism in atrial fibrillation studies in elderly (left) and total population (right)

*Event numbers for Engage-AF-Timi 48 in elderly have been estimated from published confidence intervals.

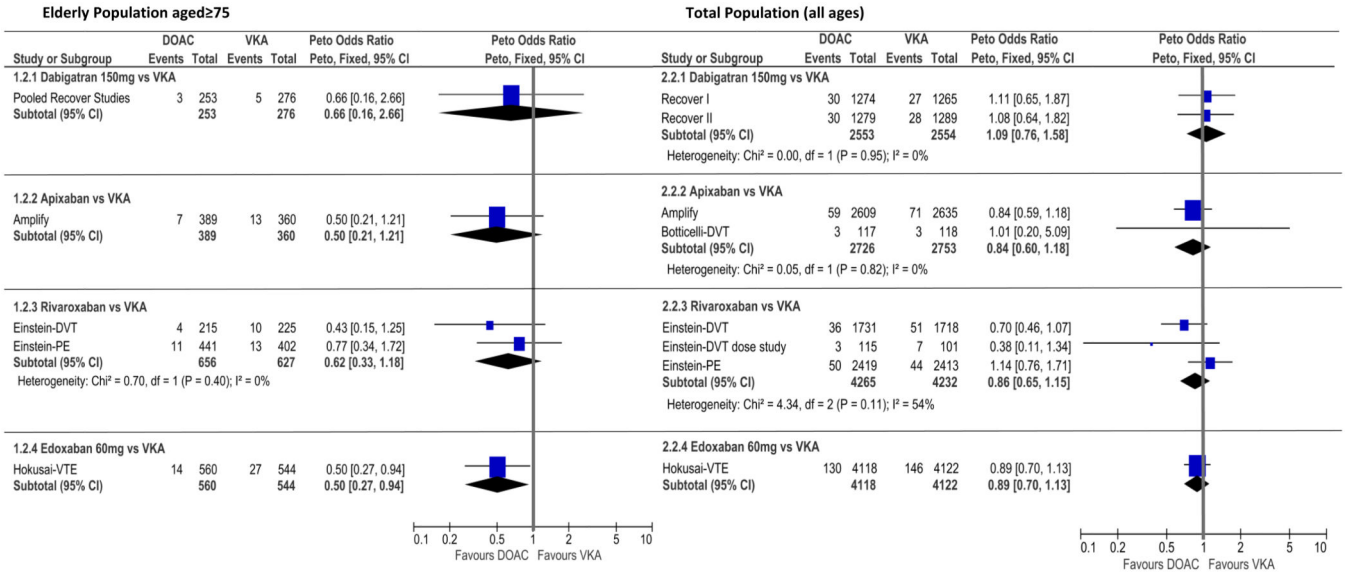

Figure 4. Risk of recurrent venous thromboembolism in venous thromboembolism studies in elderly (left) and total population (right)

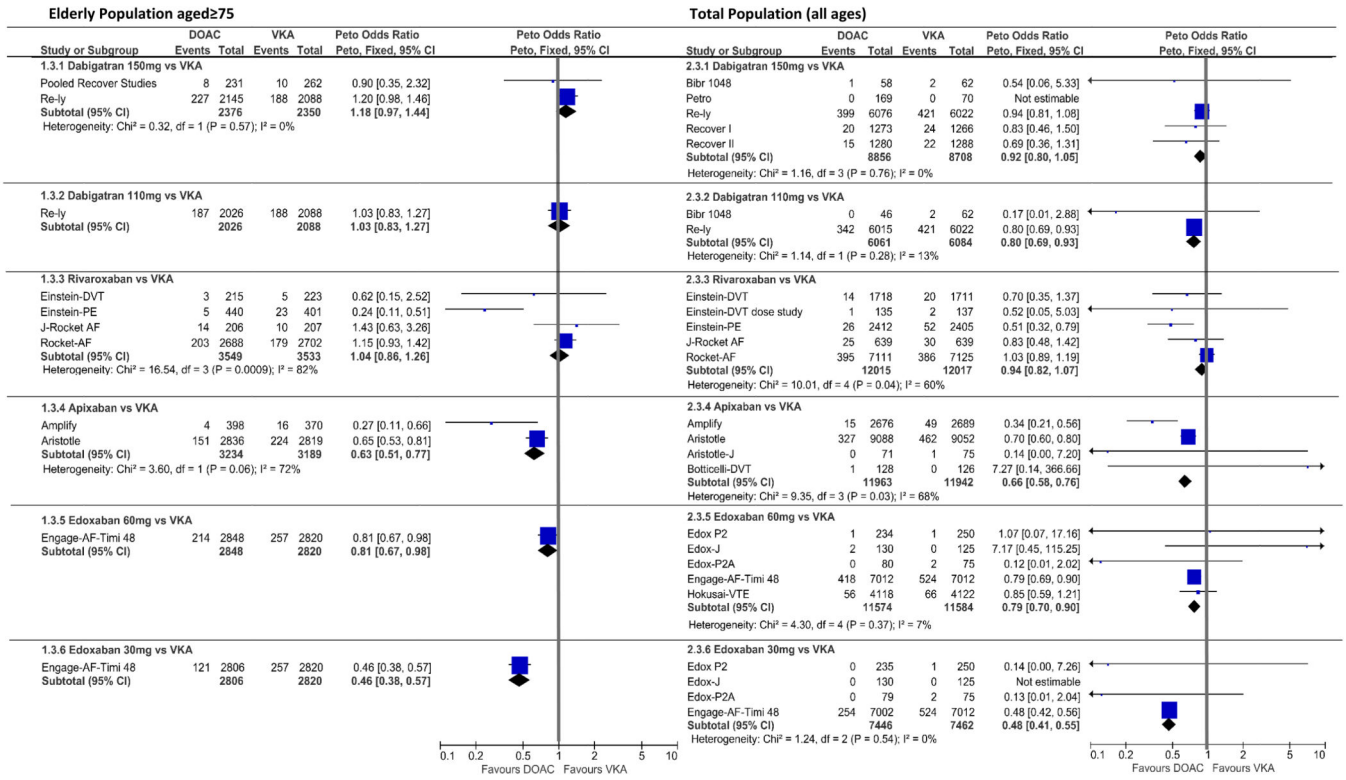

Figure 5. Risk of major bleeding in elderly (left) and total population (right)

*Event numbers for Engage-AF-Timi-48 and J-Rocket AF in the elderly have been estimated from published confidence intervals.

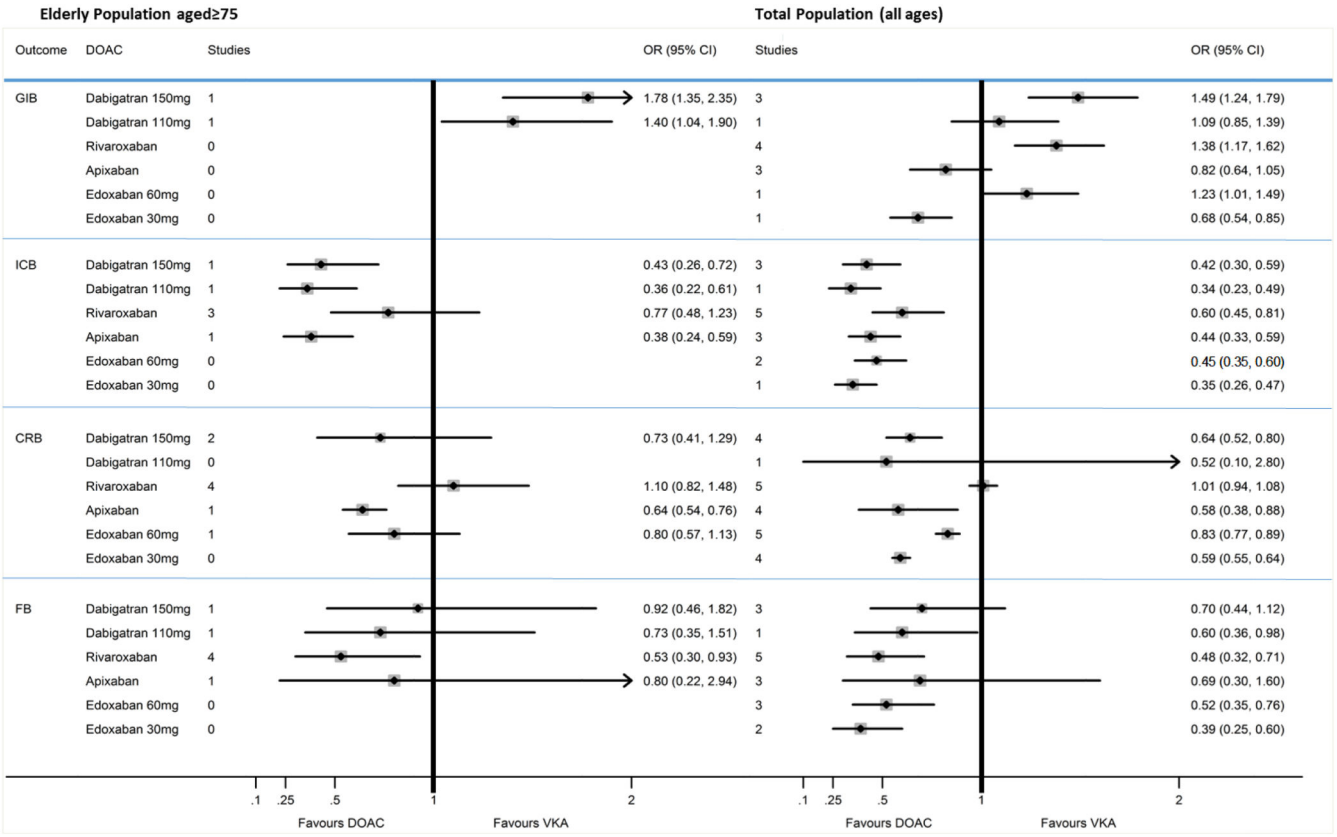

Figure 6. Risk of secondary outcomes in elderly (left) and total population (right)

GIB= Gastrointestinal bleeding; ICB = Intracranial Bleeding; CRB= Clinically Relevant Bleeding; FB= Fatal Bleeding

*CRB estimate was only estimate derived using a random effects model. **Note: Full Forest Plots for each estimate above are available in the supplementary appendix.

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Table 1

Characteristics of included studies for DOACs in atrial fibrillation and venous thromboembolism

Study	Indication	Standard Dose	Phase	Duration/Median Follow up* (months)
DABIGATRAN				
Bibr 1048, 2005[24]	AF	110mg BD or 150mg BD	II	3
Petro, 2007[30]	AF	150mg BD extracted	II	3
Re-ly, 2009[27]	AF	110mg or 150mg BD	III	24*
Recover I, 2010[28]	VTE	150mg BD	III	6
Recover II, 2013[29]	VTE	150mg BD	III	6
APIXABAN				
Aristotle, 2011[26]	AF	5mg BD	III	21.6*
Aristotle-J, 2011[32]	AF	5mg BD extracted	II	3
Botticelli-DVT, 2008[33]	VTE	5mg BD	II	3
Amplify, 2013[31]	VTE	10mg BD for 7 days then 5mg BD	III	6
RIVAROXABAN				
Rocket-AF, 2011[22]	AF	20mg OD	III	23.2*
J-Rocket AF, 2011[21]	AF	15mg OD	III	30
Einstein-DVT Dose Study, 2008[23]	VTE	20mg OD extracted	II	3
Einstein-DVT, 2010[19]	VTE	15mg BD for 21 days then 20mg OD	III	3,6 or 12
Einstein-PE, 2012[20]	VTE	15mg BD for 21 days then 20mg OD	III	3,6 or 12
EDOXABAN				
Edox-P2, 2010[36]	AF	30mg or 60mg OD extracted	II	3
Edox-P2A, 2010[25]	AF	30mg OD or 60mg OD	II	3
Edox-J, 2012[37]	AF	30mg or 60mg OD extracted	II	3
Engage-AF-Timi 48, 2013[35]	AF	30mg OD or 60mg OD	III	33.6*
Hokusai-VTE, 2013[34]	VTE	60mg OD	III	3 to 12

OD= Once daily

BD=Twice daily

Table 2

Patient Characteristics in included studies for DOACs in atrial fibrillation and venous thromboembolism

Study	Total Participants		Participants ≥75		Mean Age (SD)		Men%		$CHADS_2$ (SD)		Previous VTE (%)	
	DOAC	VKA	DOAC	VKA	DOAC	VKA	DOAC	VKA	DOAC	VKA	DOAC	VKA
DABIGATRAN												
Bibr 1048, 2005[24]	104	62	NA	NA	69.0 (8.4)	67.4 (8.8)	85.6	91.9	NA	NA	NA	NA
Petro, 2007[30]	169	70	NA	NA	70.0 (8.1)	69.0 (8.3)	81.3	84.3	NA	NA	NA	NA
Re-ly, 2009[27]	12091	6022	4815	2423	71.4 (8.7)	71.6 (8.6)	63.7	63.3	2.1(1.1)	2.1(1.1)	NA	NA
Recover I, 2010[28]	1274	1265	NA	NA	55.0 (15.8)	54.4 (16.2)	58.0	58.9	NA	NA	327 (25.7)	322 (25.4)
Recover II, 2013[29]	1279	1289	NA	NA	54.7 (16.2)	55.1 (16.3)	61.0	60.2	NA	NA	247 (19.3)	203 (15.8)
APIXABAN												
Aristotle, 2011[26]	9120	9081	2850	2828	69.1(9.6)	69.0 (9.7)	64.5	65.0	2.1 (1.1)	2.1 (1.1)	NA	NA
Aristotle-J, 2011[32]	74	74	45	23	70.0 (8.1)	71.7 (7.0)	82.4	81.1	2.1	1.9	NA	NA
Botticelli-DVT,2008[33]	130	128	NA	NA	56.0 (14.0)	59.0 (16.0)	64.0	63.0	NA	NA	37 (28.5)	31 (24.2)
Amplify, 2013[31]	2691	2704	398	370	57.2 (16.0)	56.7 (16.0)	58.3	59.1	NA	NA	463 (17.2)	409 (15.1)
RIVAROXABAN												
Rocket-AF, 2011[22]	7131	7133	3082	3082	71.2 (9.4)	71.2 (9.4)	60.3	60.3	3.5 (0.9)	3.5 (0.9)	NA	NA
J-Rocket AF, 2011[21]	640	640	252	246	71.0 (8.3)	71.2 (7.9)	82.9	78.2	3.3	3.2	NA	NA
Einstein-DVT Dose Study, 2008[23]	136	137	NA	NA	58.0	57.0	47.0	53.0	NA	NA	28 (21.0)	40 (29.0)
Einstein-DVT, 2010[19]	1731	1718	215	225	55.8 (16.4)	56.4 (16.3)	57.4	56.3	NA	NA	336 (19.4)	330 (19.2)
Einstein-PE, 2012[20]	2419	2413	441	402	57.9 (7.3)	57.5 (7.2)	54.1	51.7	NA	NA	455 (18.8)	489 (20.3)
EDOXABAN												
Edox-P2, 2010[36]	470	251	NA	NA	65.0 (8.6)	66.0 (8.5)	63.0	60.4	NA	NA	NA	NA
Edox-P2A, 2010[25]	159	76	21	10	65.4 (8.4)	64.5 (9.5)	66.6	62.7	1.9(1.0)	1.8(1.1)	NA	NA
Edox-J, 2012[37]	267	134	77	35	68.9	68.8	73.2	82.9	2.0	2.2	NA	NA
Engage-AF-Timi 48, 2013[35]	14069	7036	5654	2820	70.6(9.4)	70.5(9.4)	61.6	62.5	2.8(1.0) and 2.8(1.0)	2.8(1.0)	NA	NA
Hokusai-VTE, 2013[34]	4143	4149	560	544	55.7 (16.3)	55.9 (16.2)	57.3	57.2	NA	NA	784 (19.0)	736 (17.9)

NA= Not available

SD= Standard Deviation